that is absent or defective in a disease and wherein said RPE cells and the cells of the non-RPE cell population are attached to a matrix.

61. (Amended) A compartmentalized kit adapted to receive a first container adapted to contain retinal pigment epithelial (RPE) cells and a second container adapted to contain a non-RPE cell population, wherein said RPE cells are allogeneic to said non-RPE cell population and wherein said non-RPE cell population produces a biologically active molecule that is absent or defective in a disease.

62. (Amended) A compartmentalized kit according to claim 60, wherein the non-RPE cell population comprises insulin-producing cells.

64. (Amended) An article of manufacture, comprising:

a packaging material;

retinal pigment epithelial (RPE) cells contained within said packaging material, wherein said RPE cells are effective for creating an immune-privileged site in a mammal;

a non-RPE cell population contained within said packaging material, wherein said non-RPE cell population produces a biologically active molecule and wherein said non-RPE cell population is allogeneic to said RPE cells; and

wherein said packaging material contains a label that indicates that said RPE cells can be used for creating an immune-privileged site in a mammal.

REMARKS

Claims 33-64 are pending. Claims 33-64 were rejected under 35 U.S.C. §112, first paragraph. Claims 33-53 were rejected under 35 U.S.C. §112, second paragraph. Claims 33, 36-38, 44, 51-53, 54 and 57-59 were rejected under 35 U.S.C. §102(b). Claims 33-38, 41-45, 49,

51-61 and 64 were rejected under 35 U.S.C. §102(e). Claims 33-49, 51-61 and 64 were rejected under 35 U.S.C. §103.

Claims 33, 39-42, 45, 47-50, 54, 60-62 and 64 have been amended herein without prejudice or disclaimer of any previously claimed subject matter.

Support for the amendments can be found throughout the specification. For example, support for amendment to claim 33 is found, *inter alia*, at page 4, lines 16-35; page 6, line 35, to page 7, line 2 and in originally filed claim 3. Support for amendment to claims 33, 54, 61 and 64 is found, *inter alia*, at page 4, line 5. Support for amendment to claims 39, 41, 42, 45, 47-50, 54, 60-62 and 64 is found, *inter alia*, at page 4, lines 16-20 and 31-35 and page 6, line 35, to page 7, line 2. Support for amendment to claim 39 is found, *inter alia*, at page Support for amendment to claims 30 and 40 is found, *inter alia*, at page 5, lines 2-5 and in originally filed claims 5 and 8. Support for amendment to claim 60 is found, *inter alia*, in originally filed claim 18. Thus, the amendments to the claims do not constitute new matter.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 37, 41, 59, 62 and 64 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification is such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this ground for rejection.

With regard to claims 37 and 59, the Examiner asserts that "a second cell population that supplies an effective amount of "polypeptide growth factor, cytokine and polypeptide differentiation factor" is not disclosed as originally filed" (Office Action, page 2, section 1). However, the specification describes cells that produce therapeutic proteins including growth factors, cytokines and differentiation factors for example, at page 5, lines 12-14 and lines 24-27, and in originally filed claims 4 and 19. Thus, Applicants submit that the specification as filed conveys to one skilled in the art possession of the invention with regard to claims 37 and 59.

With regard to claim 41, the Examiner asserts that "using second cells attached to a matrix while the RPE are not attached to the matrix" is considered new matter (Office Action, page 3, section 1). On the contrary, the specification describes that either the RPE cells or the co-administered cells can be attached to a support matrix at, for example, page 12, lines 15-18 and in originally filed claims 6 and 18. Thus, Applicants submit that the specification as filed conveys to one skilled in the art possession of the invention with regard to claim 41.

With regard to claim 62, the Examiner asserts that "a second cell population of "insulin-producing cells" in the kit" is considered new matter (Office Action, page 3, section 1). At page 4, lines 31-35, the specification provides a non-limiting list of co-administered cells that produce biologically active molecules including insulin producing β-cells. In addition, the specification describes kits adapted to contain cells that produce a therapeutic molecule (see, for example, page 14, lines 34-37). Applicants submit that cells that produce a therapeutic molecule include insulin-producing cells. Thus, Applicants submit that the specification as filed conveys to one skilled in the art possession of the invention with regard to claim 62.

With regard to claim 64, the Examiner asserts that "the scope of the article of manufacture with both RPE and the second cell population as claimed was not contemplated in the original disclosure" (Office Action, page 3, section 1).

The originally filed claim 23 was directed an article of manufacture comprising packaging material and RPE cells. However, the specification clearly describes compositions and kits comprising both RPE cells and a second non-RPE cell population, for example, at page 14, lines 25-29 and lines 34-37. Thus, Applicants submit that a claim to an article of manufacture comprising both RPE cells and non-RPE cells is clearly within the scope of the invention and that the specification as filed conveys to one skilled in the art possession of the invention with regard to claim 64.

Accordingly, Applicants respectfully request that this ground for rejection be withdrawn.

Claims 33-64 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. Applicants respectfully traverse this ground of rejection.

The Examiner asserts that specification "does not reasonably provide enablement for administering RPE or RPE with non-RPE to obtain any therapeutic effect using any therapeutic protein/biologically active molecule in any disease as broadly claimed" (Office Action, page 3, section 2). Applicants submit that the invention is not as broadly claimed as the Examiner asserts.

The claimed invention is directed to methods of treating a disease responsive to a biologically active molecule in a mammal through creating an immune-privileged site in the mammal by administering retinal pigment epithelial (RPE) cells and co-administering a population of non-RPE cells to the site. The non-RPE cell population supplies the biologically active molecule that is deficient in the disease in an amount effective to sustain a therapeutic effect to the mammal. In the claimed methods, the non-RPE cells are allogeneic to the mammal. The claimed invention is also directed to pharmaceutical compositions and kits comprising RPE cells and a population of non-RPE cells in which the non-RPE cell population produces a

biologically active molecule that is absent or defective in a disease and the non-RPE cell population is allogeneic to the RPE cells.

As presented in Applicants' response submitted November 13, 2000, the specification provides examples of diseases responsive to a biologically active molecule as well as examples of therapeutic biologically active molecules and examples of cells which produce such molecules (see, for example, page 4, lines 28-35; page 5, line 27, to page 6, line 2; page 6, line 35, to page 7, line 2; page 8, line 32, to page 9, line 12). In addition, diseases responsive to administration of specific biologically active molecules and cells that produce the specific molecules were known in the art. The specification also describes administration of the cells of the invention (see, for example, page 15, line 11, to page 16, line 14) and indicates that administration of these cells is accomplished by conventional techniques. *In vivo* administration of the cells of the present invention was well-known in the art at the time of filing.[1] Thus, neither the selection of cells that produce a particular therapeutic molecule for the treatment of a particular disease nor the administration of such cells would require undue experimentation.

With regard claims 39 and 40, the Examiner states that "non-protein biologically active molecule are not enabled" (Office Action, page 7, section 2). As discussed below under 35 U.S.C. §112, second paragraph, in the interest of expediting prosecution, these claims have been amended to recite protein biologically active molecules.

Accordingly, Applicants submit that the pending claims are in compliance with the enablement requirement.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of claims under 35 U.S.C. §112, first paragraph.

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[1] For example, the Examiner points to several references which describe cells transplanted to produce therapeutic molecules on page 4 of the Office Action.

Rejections under 35 U.S.C. §112, second paragraph

Claims 33-53 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this ground for rejection.

Although Applicants believe that the claims were sufficiently definite when considered in view of the specification and the understanding of those of skill in the art, Applicants have attempted to incorporate and/or respond to each of the various suggestions of the Examiner in order to enhance clarity and to facilitate disposition of the present case.

The Examiner has asserts that claim 33 is indefinite "because it is unclear whether applicants intend to administer RPE cells alone or RPE and non-RPE" (Office Action, page 7, section 3). Applicants submit that the specification is clear to one skilled in the art that the claimed method comprises co-administering RPE cells and a second cell population made of cells other than unmodified RPE cells.

As amended, claim 33 explicitly states that the claimed method involves the co-administration of RPE cells and non-RPE cells. As noted in Applicants' response submitted November 13, 2000, the specification clearly describes embodiments in which RPE cells are administered with a second type of cell, i.e. non-RPE cells. For example, on page 6, line 36, the specification states that "RPE cells are co-administered with additional cells or tissues, such as neural cells, endocrine cells, muscle cells and other cells that produce a functionally active therapeutic molecules." Further, on page 12, line 16, the specification refers to "transplanted RPE cells or co-administered cells" (emphasis added). Thus, the specification clearly distinguishes between RPE cells and the co-administered cells. Therefore, the specification conveys to one of skill in the art that RPE cells are co-administered with non-RPE cells.

The Examiner also asserts that claim 33 is indefinite since, "[i]f two types of cells are being administered, it is unclear whether the cells are administered simultaneously" (Office Action, page 7, section 3). The Examiner acknowledges that the specification states that co-administration can be in a single composition or as separate compositions. Thus, the

specification provides for methods comprising administration of the RPE cells and the non-RPE cell population at the same time as well as administration of the two cell populations at different times.

Claim 33 has also been amended to more clearly state the connection between the disease and the biologically active molecule and the step of a therapeutic effect associated with the claimed method.

With regard to claims 39 and 40, the Examiner finds the claims indefinite "because the phrase a nucleic acid encoding said "biologically active molecule" is unclear" (Office Action, page 8, section 3). Applicants thank the Examiner for his suggestion regarding claim language with would obviate these rejections. Although Applicants submit that the phrase in question is clear to one skilled in the art, in the interest of expediting prosecution, Applicants have amended claims 39 and 40 to recite the suggested language.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 33-53 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §102

Claims 33, 36-38, 44, 51-53, 54 and 57-59 were rejected under 35.U.S.C. §102(b) as allegedly anticipated by Ye et al. (1993, *Current Eye Research*, 12:629-639) ("Ye"). Applicants respectfully traverse this ground for rejection.

As stated above, the present invention is directed to methods for treating a disease responsive to a biologically active molecule in a mammal by creating an immune-privileged site in a mammal by administering an effective amount of RPE cells and co-administering to the site a population of non-RPE cells that supplies the biologically active molecule that is deficient in the disease in an amount effective to sustain a therapeutic effect. In the claimed methods, the non-RPE cell population is allogeneic to the mammal. Pending claims are also directed to compositions comprising RPE cells and a population of non-RPE cells, wherein the non-RPE

cell population produces a biologically active molecule. In the claimed compositions, the non-RPE cell population is allogeneic to the RPE cells.

Ye describes transplantation of allogeneic RPE cells to the retina of rabbits but does not describe co-administration of RPE cells with a second cell population, *i.e.* non-RPE cells. The Examiner states that "the specification encompasses using RPE as both the RPE and second cell population" (Office Action, page 9, section 4). The pending claims are directed to compositions comprising and methods co-administering RPE cells and a population of non-RPE cells. Thus, Ye does not teach the claimed invention and, accordingly, Ye does not effectively anticipate the present invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b).

Claims 33-38, 41-45, 49, 51-61 and 64 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Cherksey (U.S. Patent 5,618,531) ("Cherksey"). Applicants respectfully traverse this ground for rejection.

Cherksey describes neural or paraneural cells, including RPE cells, attached to a matrix and administered to the brain for the treatment of Parkinson's Disease. The Examiner states that the "RPE are considered both first and second cell populations" (Office Action, page 9, section 5). As noted above, the pending claims are directed to compositions comprising and methods co-administering RPE cells and a population of non-RPE cells. Thus, Cherksey does not teach the claimed invention and, accordingly, Cherksey does not effectively anticipate the present invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(e).

Rejections under 35 U.S.C. §103

Claims 33-38, 41-49, 51-61 and 64 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cherksey. Claims 33, 39 and 40 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cherksey in view of Goldstein et al. (U.S. Patent 5,300,436) ("Goldstein"). Applicants respectfully traverse these grounds for rejection.

Applicants respectfully point out that the cited references do not support *prima facie* obviousness with regard to the claimed invention.

The present invention is directed to the use of RPE cells to create an immune-privileged site upon administration to a mammal. The immune-privileged site created by the RPE cells allows for the co-administration of non-RPE cells which are allogeneic to the mammalian recipient of the cells. Thus, the methods of the present invention comprise co-administering RPE cells and a population of non-RPE cells to a mammal in which the non-RPE cell population is allogeneic to the mammal. Pending claims are also directed to compositions and kits comprising RPE cells and a population of non-RPE cells, wherein the non-RPE cell population is allogeneic to the RPE cells.

Cherksey teaches administration of matrix-attached neural or paraneural cells, including RPE cells, to the brain. Cherksey also describes "co-culture of neural or paraneural cells with glial cells." The Examiner acknowledges that "Cherksey does not expressly teach administering RPE and a population of allogeneic non-RPE cells" but states that "Cherksey teaches transplanting a matrix having both RPE and glial cells attached to a host (column 9, line 2) and that the cells may be allogeneic to the host (column 11, line 37)" (Office Action, page 10, section 6). However, although Cherksey states that the cells useful in the methods of the invention may be allogeneic to the recipient (column 11, lines 34-40), contrary to the Examiner's assertions, Cherksey is silent with regard to the relationship of the glial cells to the RPE cells and/or to the animal recipient.

Importantly, Cherksey teaches only implantation of cells into a pre-existing immune-privileged site[2], the brain. Cherksey does not teach or suggest the use of RPE cells to create an immune-privileged site and thus, does not teach the claimed invention.

Further, as there is no teaching in Cherksey that RPE cells can create an immune-privileged site, Cherksey provides no motivation for one of skill in the art to modify the teachings therein to arrive at the presently claimed invention, the co-administration of RPE cells and allogeneic non-RPE cells.

Still further, since Cherksey describes only implantation of cells into a pre-existing immune-privileged site, one would have no expectation of success of the present invention from the teaching of Cherksey, *i.e.*, the co-administration of RPE cells with a population of allogeneic non-RPE cells, wherein the non-RPE cells supply a biologically active molecule in an amount effective to sustain a therapeutic effect to the recipient of the cells.

Accordingly, Cherksey does not support *prima facie* obviousness with regard to the claimed invention.

Goldstein teaches transfecting a tyrosine hydroxylase gene into cells, including RPE cells, and transplanting the genetically altered cells into the brain, a pre-existing immune-privileged site. Goldstein does not address the fundamental deficiencies of Cherksey in the Office's contention of obviousness and thus the Office has not met its burden to prove obviousness. Goldstein does not teach co-administration of RPE cells with non-RPE cells wherein the non-RPE cells are allogeneic to the mammalian recipient of the cells. Goldstein contains no disclosure with regard to creating an immune-privileged site with RPE cells. Thus, Goldstein in combination with Cherksey does not teach or suggest the claimed invention.

Applicants respectfully point out that the cited references do not support *prima facie* obviousness with regard to the claimed invention.

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[2] See Streilein (1995, *Science* 270:1158-1159; of record) for a list of immune privilege sites existing in the body.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' agent at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000500. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: July 24, 2001

By: 

Karen R. Zachow
Registration No. 46,332

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-5895
Facsimile: (650) 494-0792

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

33. (Amended) A method of treating a disease responsive to a biologically active molecule in a mammal, comprising:

creating an immune-privileged site in a mammal by administering an effective amount of retinal [pigmented] pigment epithelial (RPE) cells and co-administering to the site a [second cell] population of non-RPE cells that supplies [an effective amount of] the biologically active molecule that is deficient in the disease in an amount effective to sustain a therapeutic effect, wherein said [second] non-RPE cell population is allogeneic to the mammal.

39. (Amended) The method of claim 33 wherein said [second cell] population of non-RPE cells is [are cells] transformed by a nucleic acid encoding said biologically active molecule and wherein said biologically active molecule is a biologically active protein.

40. (Amended) The method of claim 33 wherein said RPE cells are transformed by a nucleic acid encoding a biologically active [molecule] protein.

41. (Amended) The method of claim 33 wherein said RPE cells or said cells of said [second] non-RPE cell population are attached to a matrix prior to administration.

42. (Amended) The method of claim 33 wherein said RPE cells and said cells of said [second] non-RPE cell population are attached to a matrix prior to administration.

47. (Amended) The method of claim 33, further comprising re-administering RPE cells or cells of said [second] non-RPE cell population to the site in an effective amount to sustain a therapeutic effect.

48. (Amended) The method of claim 33 further comprising re-administering RPE cells and cells of said [second] non-RPE cell population in amounts effective to sustain a therapeutic effect, wherein the RPE cells and the cells of the [second] non-RPE cell population are attached to a matrix prior to re-administration.

49. (Amended) The method according to claim 33 wherein the RPE cells and the [second] non-RPE cell population are co-administered as a single composition.

50. (Amended) The method according to claim 33 wherein the RPE cells and the [second] non-RPE cell population are co-administered as separate compositions.

54. (Amended) A pharmaceutical composition comprising retinal [pigmented] pigment epithelial (RPE) cells, a [second] non-RPE cell population, and a pharmaceutically acceptable carrier,

wherein said [second] non-RPE cell population is allogeneic to said RPE cells and wherein said [second] non-RPE cell population produces a biologically active molecule that is absent or defective in a disease.

60. (Amended) A pharmaceutical composition comprising retinal [pigmented] pigment epithelial (RPE) cells and a [second] non-RPE cell population, wherein said [second] non-RPE cell population is allogeneic to said RPE cells, wherein said [second] non-RPE cell population produces a biologically active molecule that is absent or defective in a disease and

wherein said RPE cells and the cells of the [second] non-RPE cell population are attached to a matrix.

61. (Amended) A compartmentalized kit adapted to receive a first container adapted to contain retinal [pigmented] pigment epithelial (RPE) cells and a second container adapted to contain a [second] non-RPE cell population, wherein said RPE cells are allogeneic to said [second] non-RPE cell population and wherein said [second] non-RPE cell population produces a biologically active molecule that is absent or defective in a disease.

62. (Amended) A compartmentalized kit according to claim 60, wherein the [second] non-RPE cell population comprises insulin-producing cells.

64. (Amended) An article of manufacture, comprising:

a packaging material;

retinal [pigmented] pigment epithelial (RPE) cells contained within said packaging material, wherein said RPE cells are effective for creating an immune-privileged site in a mammal;

a [second] non-RPE cell population contained within said packaging material, wherein said [second] non-RPE cell population produces a biologically active molecule and wherein said [second] non-RPE cell population is allogeneic to said RPE cells; and

wherein said packaging material contains a label that indicates that said RPE cells can be used for creating an immune-privileged site in a mammal.